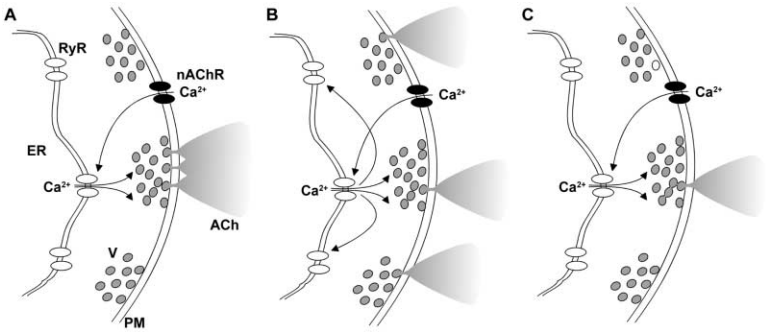

Figure 1. Schematic of Three Possible Origins of Multiquantal Minis

(A) Multiple vesicle fusions at one active zone.
(B) Synchronous release from neighboring active zones.
(C) Compound vesicle fusion.
Abbreviations: Ca^{2+}, calcium ions; ER, endoplasmic reticulum; RyR, ryanodine receptor; PM, plasma membrane; nAChR, nicotinic acetylcholine receptor; V, vesicles; ACh, acetylcholine.

minis include a demonstration that they can be desynchronized into their component parts, for example by low temperature, or that they are resistant to the stimulatory action of sucrose, which should act downstream of any synchronizing process.

How can this spontaneous synchronization of quantal elements come about? One could imagine that a very local rise in $[Ca^{2+}]_i$ due to CICR activates multiple vesicular fusions at one release site (Figure 1A), but Sharma and Vijayaraghavan argue against this because of the apparent imperfect synchrony in the longer rise times of large minis. They propose a somewhat less localized $[Ca^{2+}]_i$ rise activating several neighboring active zones nearly simultaneously (Figure 1B). A third possibility might be compound exocytosis (Parsons and Sterling, 2003), caused by the high $[Ca^{2+}]_i$ levels reached at the back of active zones distant from the plasmalemma and its Ca^{2+} channels (Figure 1C). Distinguishing these alternatives will no doubt be the subject of further work on this synapse. Recording the local $[Ca^{2+}]_i$ blips that are inferred to underlie large minis, perhaps by use of fast confocal scanning microscopy or two-photon scanning microscopy (Emptage et al., 2001; Llano et al., 2000), and correlating them with the occurrence of large minis might provide further mechanistic insight into how they arise.

Beyond mechanism lies the further question of function. Sharma and Vijayaraghavan showed that enhancement of mini frequency, and apparent synchronization, can together have a strong effect on a postsynaptic cell, driving it to fire a prolonged high-frequency burst in response to focal application of 20 μM nicotine. It will be important to determine whether a presynaptic action of acetylcholine in exciting synaptic transmission occurs with endogenous cholinergic input. It will be also be interesting to find out whether nicotine levels occurring in smokers have similar effects and whether this contributes to nicotine toxicity. If such a mechanism for generating a meaningful synaptic signal out of quantal noise can be shown to occur in vivo in a physiologically relevant context, it will provide an important addition to the repertoire of mechanisms of neuronal plasticity.

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Ocular Dominance Plasticity in Mature Mice

Ocular dominance plasticity, classically thought to be restricted to an early critical period, is now described by Sawtell et al. in fully adult mice. Adult plasticity, like critical period plasticity, requires cortical NMDA receptors but involves different functional changes in cortical circuits.

Much of our understanding of how sensory experience shapes circuit function derives from the study of ocular dominance in primary visual cortex (V1). Ocular dominance is the relative response of a neuron to visual stimulation of the right versus the left eye. As first shown in the cat and monkey, closing one eye for a brief period (monocular deprivation, MD) causes a lasting shift in ocular dominance toward the open eye (Hubel, 1982). In these classic experiments, plasticity occurred only when MD was begun during a narrow age range in the

first few weeks or months of life, termed the critical period. Many forms of plasticity and learning have since been described as confined to critical periods, including imprinting in chicks, language learning in humans, and song learning in birds.

However, recent evidence suggests that most critical periods do not close abruptly and absolutely, but gradually and often incompletely. For example, the capacity for rapid plasticity in somatosensory (S1) cortex declines sharply in some cortical layers soon after birth, but persists in others into adulthood (Diamond et al., 1994; Glazewski and Fox, 1996), and a similar pattern has been observed for ocular dominance plasticity in some species (Daw et al., 1992). Correspondingly, sensory deprivation or behavioral training can induce substantial plasticity even in adults (reviewed in Buonomano and Merzenich, 1998). Whether critical period and adult plasticity share common cellular and molecular mechanisms is unclear. In a new paper, Sawtell and colleagues (2003) demonstrate for the first time that ocular dominance plasticity occurs in adult mice and uses different mechanisms than plasticity during the classical critical period.

Previous extracellular unit recording studies showed that neurons in the small binocular zone of mouse V1 exhibit a range of ocular dominance, though cells dominated by contralateral eye inputs outnumber those dominated by ipsilateral eye inputs. Such contralateral bias is common across species but is particularly strong in mouse. Brief periods (3–4 days) of MD cause ocular dominance plasticity, but only within a well-defined critical period ending at ~35 days of age (Gordon, 1997). Sawtell et al. reexamined the critical period by measuring the mean ocular dominance of neurons in the binocular zone as the ratio of visually evoked potentials (VEPs) elicited by visual stimulation of the contralateral versus the ipsilateral eye. Initial experiments were performed in anesthetized mice. Consistent with previous results, VEPs showed a strong contralateral eye bias in mice raised with normal visual experience. Brief MD (3 days) caused the ratio of open eye to closed eye VEPs to increase significantly in the hemisphere ipsilateral to the open eye, indicating a shift in mean ocular dominance toward the open (ipsilateral) eye. For brief MD, ocular dominance plasticity occurred only during the classical critical period, as expected. Surprisingly, however, a slightly longer duration of MD (5 days) elicited significant ocular dominance plasticity, more than half the magnitude seen in young animals, even in fully mature mice 90 days of age.

The basis for this remarkable adult plasticity was studied by daily VEP recordings from chronically implanted electrodes in awake animals, which allowed ocular dominance and the strength of right eye and left eye inputs to be tracked over time at single recording sites. As in anesthetized mice, 5 days of adult MD caused a large ocular dominance shift in the hemisphere ipsilateral to the open eye, whereas 3 days of adult MD elicited no significant plasticity. The adult ocular dominance shift was due almost exclusively to an increase in absolute amplitude of ipsilateral (open) eye VEPs, rather than a decrease in amplitude of contralateral (closed) eye VEPs. This suggests that adult MD was due to the active strengthening of initially weak ipsilateral inputs in response to closure of the contralateral, dominant eye. Strengthening of ipsilateral inputs developed gradually over the first 3–6 days of MD, explaining why brief MD fails to elicit ocular dominance changes in adult mice. Why strengthening proceeds more slowly than weakening is unknown, but may reflect a requirement for metaplasticity (an activity-dependent change in the induction requirements for synaptic plasticity) before actual synaptic strengthening can occur (Bear et al., 1987; Sawtell et al., 2003).

In young mice, in contrast, 3 days of MD caused a rapid ocular dominance shift and did so by the converse mechanism: the amplitude of contralateral (closed) eye VEPs rapidly decreased, whereas ipsilateral (open) eye VEPs did not change. Together, these results indicate that rapid weakening of deprived eye inputs is the primary mechanism for ocular dominance plasticity in young mice, whereas plasticity in adults involves different circuit-level mechanisms including the strengthening of open eye inputs. Both weakening of deprived inputs and strengthening of open eye inputs were long predicted from classical MD studies using single-unit recording (Hubel, 1982). However, a separation of these phenomena by age is unexpected and promises to greatly aid discovery of their synaptic basis.

To determine if adult plasticity, like juvenile plasticity, was mediated by cortical N-methyl-D-aspartate (NMDA) receptors, Sawtell et al. created an adult-onset, cortex-specific NMDA receptor subunit-1 knockout (CxNR1KO) mouse that lacked functional NMDA receptors in most visual cortical pyramidal cells, starting after 30 days of age. (NMDA receptor expression was intact in thalamus and in inhibitory V1 neurons). Though baseline ocular dominance and spatial acuity were normal in CxNR1KO mice, adult ocular dominance plasticity was essentially absent. Thus, adult ocular dominance plasticity requires cortical NMDA receptors, as previously shown for juvenile plasticity (Roberts et al., 1998), even though adult plasticity involves different functional changes in V1 circuits.

What might be the synaptic mechanisms for weakening and strengthening of VEPs? A dominant hypothesis is that sensory map plasticity involves NMDA receptor-dependent long-term potentiation (LTP) and depression (LTD) of cortical synapses (Bear et al., 1987; Gordon, 1997; Rittenhouse et al., 1999). A reasonable speculation is therefore that weakening of deprived eye VEPs in young mice reflects LTD and/or loss of synapses on excitatory, deprived eye pathways, while strengthening of open eye VEPs during adult MD reflects LTP or addition of synapses on open eye pathways. Thus, one prediction of the current study is that juvenile plasticity preferentially involves LTD, while adult plasticity preferentially involves LTP. Whether this is true, and which specific V1 synapses may undergo plasticity during MD, is currently debated.

Remarkably similar results have been observed during map plasticity in S1, suggesting common plasticity mechanisms. Neurons in the whisker region of rat S1 respond most strongly to tactile deflection of a single, "principal" whisker and less strongly to surrounding whiskers. Transient deprivation of the principal whisker and all but one neighboring whisker, a manipulation analogous to closing the contralateral, dominant eye, causes S1 neurons to become driven primarily by the

spared neighboring whisker. In juvenile rats, such plasticity involves both a rapid, activity-dependent weakening of deprived whisker responses and, independently, a slower increase in responses to the spared neighboring whisker (Glazewski and Fox, 1996). In adult rats, the same manipulation drives only the slow increase in spared whisker responses, and weakening is absent (Glazewski et al., 2000). Thus, both S1 and V1 plasticity involve rapid weakening of deprived inputs in juveniles and slower strengthening of spared inputs in adults. Indeed, the only substantial difference between these systems is that juvenile plasticity in V1 primarily involves rapid weakening with no apparent strengthening of open-eye responses, while in S1 it involves both weakening and slower strengthening. However, this difference may be illusory, as Sawtell et al. cite unpublished observations indicating that longer durations of juvenile MD eventually lead to strengthening of open eye inputs.

Study of the separate components of plasticity in S1 has led to tentative identification of mechanisms for experience-dependent strengthening and weakening of inputs, which may have implications for V1. Weakening of deprived whisker responses is associated with measurable, LTD-like synaptic weakening on excitatory, deprived-whisker pathways, suggesting that it represents, in part, LTD induced by whisker deprivation (Allen et al., 2003). Strengthening of spared whisker responses is selectively blocked in both adults and juveniles by a mutation in αCaMKII that prevents LTP, suggesting that it represents LTP (Glazewski et al., 2000). A similar analysis in V1 may lead to detailed hypotheses about the synaptic basis for distinct components of ocular dominance plasticity.

Thus, the current results in V1, together with prior findings in S1, suggest that competitive plasticity in juvenile sensory cortex primarily involves rapid weakening (perhaps LTD) of deprived inputs, while similar plasticity in adults is driven instead by slower strengthening (perhaps LTP) of spared inputs. If this is true, then loss of the capacity for synapse weakening, perhaps due to developmental downregulation of LTD, may be partially responsible for the closure of the critical period. Why strengthening of inputs should be slower than weakening is not fully clear, but it will be essential to understanding why post-critical period plasticity, which relies on strengthening, is often slower and more limited than critical period plasticity (Daw et al., 1992; Glazewski et al., 2000). Identification of these separate components of plasticity in V1 by Sawtell et al. should facilitate discovery of their underlying synaptic and molecular mechanisms.

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